Modeling of Dose-Response Relationships

by Bernard Altshuler*

The main dose-response models for chronic toxicity are considered. For dichotomous response, the log probit, multi-hit, and multistage models are presented. For time-to-occurrence response, the log-normal and three variations of multistage models are presented. Finally, the Cornfield hockey-stick model is considered, and, for low-dose extrapolation, it is suggested that response be taken to be proportional to dose and to a power of time determined by background response.

Introduction

The focus of this paper is on chronic toxicity with irreversible components and in particular on cancer. It presents the more important dose-response functions, which are of two kinds: dichotomous response and timed response.

In dichotomous response, the outcome of a single animal trial is either "yes, with cancer" or "no, without cancer;" the animal is either a responder or a nonresponder. Response of an experimental group of animals is the fraction of responders.

Timed response refers to the measurement of the experimental life of the animal which is terminated by the occurrence of cancer or the occurrence of some noncancer event and are described by time-to-occurrence models. The situation involves competing risks. Death without cancer preempts the subsequent occurrence of cancer and complicates the experimental results. However, the complications of competing risks are not discussed. Here, it is simply assumed that every animal is destined to get cancer if it lives long enough so that there is a potential time-to-occurrence for each animal. Thus it is meaningful to speak of a distribution of times to occurrence in the animal population. Correcting for premature deaths, the dichotomous response can be obtained as the fraction of responders at a preset time.

The main point of dealing with timed response is that cancer is an evolutionary process in time. Its theoretical basis should therefore be concerned with progression in time. In particular, the multistage dichotomous model is to be understood by its derivation from the multistage time-to-occurrence model.

It is desirable to be able to derive the models from a theoretical understanding of the biological mechanisms. Unfortunately, the theory is not well enough established, and, for the most part, dose-response models should be regarded as empirical forms chosen because of their fits to the data. Since these models are used for low-dose extrapolation outside the experimental range of doses, one needs to know the behavior of the functions at low doses and form some judgment as to their relative credibilities (1-5).

Dichotomous Response Models

The dichotomous response function is a probability distribution function $P(d)$, where d is a generic dose quantity: total dose, dose rate, daily dose or concentration. In chronic exposure, d usually means dose rate. The response function for responders is the combined effect of induced response and background response and this relationship needs to be specified. Two different cases will be considered, each specifying the same form of the response function $P(d)$ to be presented in the subsections.

In case 1, the case of independence, the induced response $P(d)$, d = dose, is independent of back-

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ground response P_0, and it follows that

$$P_0 + (1 - P_0) P(d) = \text{fraction of responders}$$

This expression is often described as Abbot's correction.

In case 2, the case of dose equivalence, total response depends on background in such a manner that background response can be regarded as induced by an equivalent background dose d_0 of the toxic substance. Thus, in this case, the induced response is $P(d) - P(d_0)$ where

$$P(d) = \text{fraction of responders}$$

and the dose quantity is

$$d = \text{dose} + d_0$$

Log Probit Response

The log probit response $P(d)$ is the cumulative probability function for the normal distribution with log dose as the distributed variable, i.e.,

$$P(d) = \frac{1}{\sqrt{2\pi} \log \sigma_g} \times$$

$$\int_{-\infty}^{\log d} \exp\left\{ -\tfrac{1}{2} \left(\frac{x - \log d_{50}}{\log \sigma_g} \right)^2 \right\} dx$$

$$(1)$$

where d_{50} is the median, or geometric mean, and σ_g is the geometric standard deviation. It has the property that, at low doses, response decreases faster with decreasing dose than any positive power of dose. This form of response is associated with the classic deterministic approach of the toxicologist. Each animal has its unique susceptibility expressed as a tolerance dose d. This means that, if dose is less than d, the animal does not respond; if dose is greater than d, the animal does respond. The log probit response is then interpreted as saying the logarithm of the tolerance dose is normally distributed.

It is an empirical fact that the log probit is a good fit in a great many biological situations. Indeed it is almost universally regarded as a reasonable approximation. It is this experience which justifies its application, but this is hardly a theoretical basis, and one must recognize that tails of the distribution are not expected to be good fits.

With a normal distribution, one naturally thinks

of the Central Limit Theorem which states the following: consider a sequence of independent random variables (distributed variables) and consider the sum of a finite subsequence; when the number of variables being summed is sufficiently large, the sum will be distributed approximately normally with minor restriction on how the individual variables are distributed.

Now, suppose tolerance is proportional to the sum or product of many factors, each of which is independently distributed among the population. Then it is plausible that tolerance or log tolerance would be normally distributed depending on whether the factors are additive or multiplicative. Still this is not biological justification; almost nothing has been said about the process.

The Multi-hit Response

The gamma distribution function

$$P(d) = \frac{1}{\Gamma(k)} \int_0^{\theta d} x^{k-1} e^{-x} dx \qquad (2)$$

can also provide a good fit to data (6).

It can be derived from the assumption that there is a discrete change, called a hit, which has to occur several times in order to produce the response. The expected number of hits is proportional to dose and equal to θd. The number of hits is given by Poisson statistics and Eq. (2) gives the probability of at least k hits with $\Gamma(k) = (k - 1)!$

For an empirical fit, k does not have to be an integer. $\Gamma(k)$ is the gamma function defined by the integral when the upper limit, θd, is infinite.

The important feature of this response is its behavior as the kth power of dose at low doses, i.e., $P(d) \simeq (\theta d)^k / \Gamma(k)$ as $d \to 0$.

When $k = 1$, the response becomes the one-hit function (3)

$$P(d) = 1 - e^{\theta d} \qquad (3)$$

which is linear at low dose, i.e., $P(d) \simeq \theta d$.

Multistage Dichotomous Response

Derived from the multistage time-to-occurrence model discussed later (7), the response function is

$$P(d) = 1 - \exp\{ - (a_1 d + \ldots + a_k d^k) \} \qquad (4)$$

where all coefficients a_i are nonnegative. Here k is the number of discrete transitions in the cancer

process which are dose-dependent. Since a_1 is positive as required by spontaneous (background) transition rates, this response approximates a one-hit response at low dose, i.e.,

$$P(d) \simeq 1 - e^{-a_1 d}$$
(5)

Time-to-Occurrence Models

Each animal is assumed to have a potential time-to-occurrence T whose distribution is given by a cumulative probability function representing the fraction of responders with T less than or equal to a time t. As was done for the dichotomous models, two cases will be considered for defining the response function $P(t;d)$.

In case 1, assuming induced response is independent of background response $P_0(t)$, it is given by

$$P_0(t) + [1 - P_0(t)] P(t;d) = \text{Prob}\{T \leq t; d = \text{dose}\}$$
(6)

In case 2, assuming an equivalent background dose d_0 for background response, the fraction of responders is

$$P(t;d) = \text{Prob}\{T \leq t; d = \text{dose} + d_0\}$$
(7)

Lognormal Model

Time-to-occurrence data are generally well fitted by the lognormal distribution function

$$P(t;d) = \frac{1}{\sqrt{2\pi} \log \sigma_g} \times$$

$$\int_{-\infty}^{\log t} \exp\left\{ -\tfrac{1}{2} \left(\frac{x - \log t_{50}}{\log \sigma_g} \right)^2 \right\} dx$$
(8)

with median time t_{50} related to dose d by the equation

$$d \, t_{50}^{n} = \text{constant}$$
(9a)

or, equivalently,

$$\log t_{50} = \text{constant}/n - \log d/n$$
(9b)

When geometric standard deviation σ_g is assumed to remain constant, the model has been applied by Albert and Altshuler (8), who refer to it as the Blum-Druckrey model. With t fixed, the dichotomous log probit response is obtained, where log d is the normally distributed variable (9).

In a plot of response P against log t, the effect of a change in dose is to shift the curve horizontally along the time axis, parallel to itself. This property is important irrespective of the form of the response function.

The Multistage Model

The multistage model is based on real biological premises. It was first proposed by Armitage and Doll (10) to explain epidemiological data which showed incidence rates increasing with a rather high power of time. The simplest formulation arises from the following assumptions: (1) A tumor develops out of a single transformed cell. (2) It takes a time w for the transformed cell to grow into an observable tumor. Thus there is no response until time t is greater than the delay w, and time-to-transformation is time-to-tumor less the delay w. (3) A target cell becomes transformed by k discrete changes which advance the cell through a sequence of stages. (4) The timing of the discrete changes, called transitions, is governed by transition rates which do not change with time. (5) Background response is governed by the spontaneous transition rates. (6) The number of dose dependent transitions, m, may be less than the number of transitions, k.

The expression $-\log[1 \times P(t;d)]$ is the cumulative hazard, which is the same as cumulative incidence. Its derivative is hazard rate or incidence rate. From the assumptions, it follows that cumulative hazard is proportional to the kth power of time and to the product of the transition rates. If each of the m dose-dependent transition rates is proportional to dose, cumulative hazard varies as the mth power of dose and the resulting expression is a Weibull distribution

$$-\log[1 - P(t;d)] = ad^m(t - w)^k$$
(10)

where a is the constant of proportionality.

As first pointed out by both Armitage and Peto and published by Crump et al. (7), if the dose-dependent transition rates are linear functions of d, i.e., a constant plus a constant times dose, then the product of all these linear functions is a polynomial in d of degree m, and this leads to the more flexible expression

$$-\log[1 - P(t;d)] = (a_1d + \ldots + a_md^m)\,(t - w)^k$$
(11)

Fixing t results in the multistage dichotomous model.

Hartley and Sielken (11) generalized further by introducing a polynomial in time to get a better temporal fit, but without biological basis. Their response function is

$$-\log[1 - P(t;d)] =$$
$$(a_1d + \ldots + a_md^m)\,[b_1\,(t - w) + \ldots + b_k(t - w)^k]$$
(12)

It also implies the multistage dichotomous model.

The form of the response function holds under more general and perhaps more realistic assumptions. For example, clonal growth may occur in intermediate stages and transition rates may be time dependent.

It is also to be noted that a change in dose will shift the plotted curve vertically in the direction of the hazard or incidence axis, which means the time pattern of incidence rates does not change with dose. This is very different from the time shift of the lognormal model and the distinction is important for low dose extrapolation.

Low-Dose Quasi-Threshold Response

Cornfield (12) has suggested the hockey-stick type of response function, illustrated in Figure 1, based on a kinetic theory of activation and deactivation mechanisms. A quasi-threshold, represented by the solid black dot, is determined by the dose
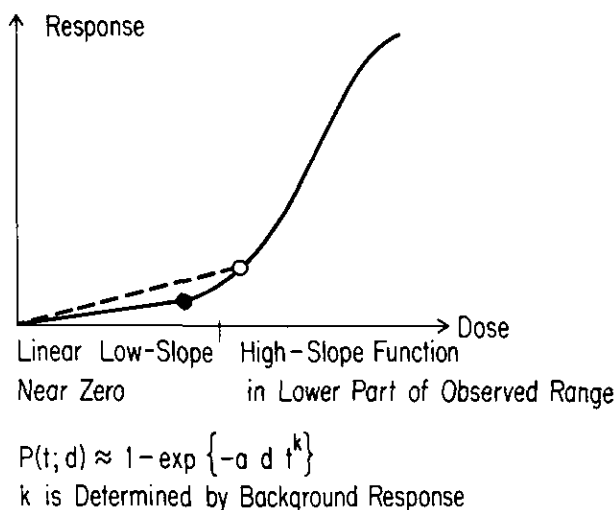
which just saturates the deactivation mechanism. His kinetic theory may not be acceptable, but it is important to recognize that this hockey-stick curve does agree with two main features of the dose-response curve as many people picture it. First, near zero, the curve is linear with such a low slope that a positive response is not detected by experimental observation. Secondly, in the dose range where positive response is observed, the slope is relatively high. Thus, if the open circle represents lowest dose with a statistically significant response, the dotted line connecting it to the origin is above the true response curve.

It is fitting to close this paper with reference to a low-dose time-to-occurrence model proposed by the Environmental Protection Agency (13). It does not pretend to be more than a rough ballpark approximation and perhaps it should not be given the aura of a formal model, but we also have to recognize all the models are rough approximations at low doses. Shown at the bottom of Figure 1 is the Weibull distribution with cumulative hazard proportional to the first power of dose and the kth power of time. EPA used $k = 3$. However, as also noted in Figure 1, k should really be determined by the time dependence of background response.

EPA has proposed to determine the proportionality constant a from the response at the smallest dose with a significant observed effect, as illustrated by the open circle.

FIGURE 1. Quasi-threshold response.

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